23. The targeted agent or protein of any of claims 1 or [2] 3, wherein the optimized, [high affinity polyamino acid] surface loop is a complementarity determining region of an antibody molecule.

24. The targeted agent or protein of claim 23, wherein the complementarity determining region is heavy chain complementarity determining region 3 (HCDR3) of monoclonal antibody Fab-9.

Please add the following new claim:

--65. The protein of claim 3, wherein the protein is loop-grafted tissue type plasminogen activator (LG-tPA).--

Please cancel claim 2 without prejudice.

REMARKS

Claims 1-24 are pending in the present application. Claims 1 and 3-24 are amended herein for clarity and to more particularly define the invention, for the reasons and with the support stated below. Claim 2 is canceled herein without prejudice. Claim 65 is added herein. It is believed that no new matter has been added by these amendments or new claim. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application , entry of the new claim and allowance of the pending claims to issue.

I. Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequence

The specification has been amended herein in response to the Notice to Comply With

Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Enclosed herewith is a diskette containing the substitute Sequence Listing in this application in computer readable form (CRF) and a substitute paper copy of the Sequence Listing in compliance with 37 C.F.R. §§ 1.821-1.825. Applicants hereby certify that the information in the computer readable form on the diskette and in the hard copy of the Sequence Listing is the same and includes no new matter. The enclosed computer readable copy and paper copy of the Sequence Listing are believed to bring the Sequence Listing into full compliance with the sequence rules.

II. Specification

The Office Action states that sequences appear in the specification, for example on page 34 of the specification at lines 25 and 27 and that applicants are required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification.

Applicants point out that on page 34, line 27, reference is made to "a HCDR-3 sequence". HCDR-3 stands for "high complementarily determining region," that is a type of sequence and is not a specific amino acid sequence requiring identification with a SEQ ID NO.

The specification is amended herein on pages 6, 34 and 37 to identify each reference to a specific amino acid sequence by the appropriate sequence identification number. Thus, applicants believe that the Examiner's comments regarding sequence identifiers have been adequately addressed and respectfully request entry of these amendments and withdrawal of this objection.

III. Claims

The Office Action states that sequences appear in claim 24 and that Applicants are

required to amend the claims to list the appropriate SEQ ID NOS for sequences disclosed in the claims.

Applicants point out that in claim 24, reference is made to "a HCDR-3 sequence". HCDR-3 stands for "high complementarity determining region," that is a type of sequence and is not a specific amino acid sequence requiring identification with a SEQ ID NO. Thus, Applicants believe this objection is moot and respectfully request its withdrawal.

IV. Priority

The Office Action states that the application appears to claim subject matter disclosed in prior copending Application No. 60/009,028 filed 12/21/95 and that a reference to the prior application must be inserted as the first sentence of the specification of this application if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120.

The specification has been amended herein to include the appropriate statement of priority in the first sentence of the specification of this pending application. Thus, applicants believe that the Examiner's comments regarding priority have been adequately addressed and respectfully request entry of this amendment to the specification and withdrawal of this objection.

V. Oath or declaration

The Office Action states that a new oath or declaration in compliance with 37 C.F.R. 167(a) identifying this application by application number and filing date is required. The oath or declaration is allegedly defective because the declaration is defective in claiming priority to PCT/US96/20577 under 35 U.S.C. 119a-d and that the priority claim should be made under 35 U.S.C. 120.

Applicants provide herein a new Declaration claiming priority to PCT/US96/20577 under Title 35, United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) or §365(b) of any PCT international application which designated at least one country other than the United States of America. Applicants believe this new Declaration overcomes the objection raised by the Examiner and respectfully request its withdrawal.

VI. Rejections under 35 U.S.C. § 102(b)

A. The Office Action states that claims 2-24 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Smith et al. (*J. Biol. Chem.*, Vol 270, 1995, pages 30486-30490) as evidenced by Barbas et al. (*PNAS,* Vol. 90, 1993, 10003-10007) and Gething et al. (*EMBO Journal*, Vol. 7, 1988, pages 2731-2740).

As suggested by the Examiner, the application is amended herein to perfect Applicant's priority claim to U.S. Provisional Application Serial No. 60/009,028, filed December 21, 1995. Therefore, the Smith et al. reference, published on December 22, 1995, should be removed as a reference under 35 U.S.C. § 102(b). Applicants believe that the removal of the Smith et al. reference overcomes the present rejection and respectfully request its withdrawal.

B. The Office Action states that claims 2, 4-13 and 15-16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Paoni et al. (*Protein Eng.*, Vol.6, 1993, pages 529-435) as evidenced by Gething et al. (*EMBO Journal*, Vol. 7, 1988, pages 2731-2740).

As stated above, Claim 2 is canceled herein without prejudice. Claims 4-13 and 15-16 are amended herein to no longer depend from Claim 2. Thus, Applicants believe that this rejection has been overcome and respectfully request its withdrawal.

VII. Rejections under 35 U.S.C § 103(a)

The Office Action states that Claims 1-24 are rejected under 35 U.S.C § 103(a) as allegedly being unpatentable over Bode et al. (*Circulation*, Vol. 84, 1991, pages 805-813) in view of Barbas et al. (*PNAS*, Vol. 90, 1993, pages 10003-10007) and further in view of Todd et al. (Clinical Diagnosis and Management by Laboratory Methods, 1979, Vol. 1, page 252), Johannessen et al. (*Thrombosis and Haemostasis*, Vol. 63, 1990, pages 54-59) and Gordon et al. (*J. Med. Chem.* Vol 37, 1994, pages 1386-1401).

The Office Action also states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have arrived at the claimed invention because of the teaching of Bode et al. of plasminogen activator linked to an antibody specific for a platelet membrane glycoprotein and because of the teaching of Barbas et al. of Fab-9 and of the importance of platelet adhesion in atherosclerotic plaques mediated by integrin $\alpha_{IIb}\beta_3$ and the teaching of Todd et al. of the importance of plasminogen activators in fibrinolysis.

Further stated in the Office Action is that one of ordinary skill in the art at the time the invention was made, would have been motivated to substitute for the 7E3 antibody in the invention of Bode et al. another platelet specific antibody such as the Fab-9 antibody taught by Barbas et al. and that one would also have been motivated to use an anti-platelet antibody specific for integrin $\alpha_{IIb}\beta_3$ such as Fab-9 particularly given the teaching of Barbas et al. that integrin $\alpha_{IIb}\beta_3$ exacerbated an artherosclerotic lesion by enabling platelet adhesion and thrombus formation at the existing atherosclerotic plaque and teaching the design of anti-receptor antibodies, specifically $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$ by protein loop grafting of RGD. Also stated in the Office Action is that one of ordinary skill in the art at the time of the invention would have been motivated to substitute another type of plasminogen activator such as t-PA for the plasminogen activator, urokinase, in the invention of Bode et al., particularly in light of the teaching of Johannesen et al. of the high efficacy and specificity of t-PA and the need for increasing the

circulatory half-life of t-PA administered by itself. In addition, claim 1 is included because one of ordinary skill in the art at the time the invention was made would have been motivated to use an isolated peptide mimetic as taught by Gordon et al. based on an optimized high affinity polyamino acid as taught by Barbas et al. and wherein the mimetic specifically binds a selected target.

The Office Action further alleges that it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because the usefulness of plasminogen activators linked to antibodies specific for platelets, as taught by Bode et al., was known in the art at the time the invention was made, the role of plasminogen activators in reducing thrombolysis and the role of platelets in thrombus formation and maintenance was known in the art, as taught by Todd et al., Bode et al., Johannessen et al. and Barbas et al., and monoclonal antibodies specific for platelet $\alpha_{IIb}\beta_3$ or $\alpha_V\beta_3$ integrins, such as Fab-9, were known in the art, as taught by Barbas et al. Furthermore, protein loop grafting to create optimized high affinity polyamino acids was well known in the art and in specific, protein loop grafting involving RGD integrin recognition sequences was also known. Therefore, according to the Office Action, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In response, Applicants restate that Claim 2 is canceled herein without prejudice and its dependent Claims 4-13 and 15-16 are amended herein to no longer depend from Claim 2, thus rendering this rejection moot as to those claims.

Furthermore, Claim 1 as amended herein recites a targeted therapeutic or diagnostic agent comprising (a) a therapeutic or diagnostic functional entity linked to (b) an isolated peptide mimetic which is based on an optimized protein surface loop and wherein the mimetic specifically binds a selected target. Support for this amendment can be found on page 12, lines

9-11 of the specification, where it is stated that one can model predicted chemical structures to mimic the structure of a binding region, such as a protein surface loop.

Applicants respectfully point out that a "surface loop," as defined on page 12, lines 19-21of the specification, is a flexible loop structure in the native protein of about 2 to about 20 amino acids. Therefore, an "optimized protein surface loop" is not an antibody such as the 7E3 antibody disclosed in the Bode et al. reference or the Fab-9 antibody taught by Barbas et al., which are much larger proteins. One skilled in the art would not have been motivated to substitute an optimized surface loop for the 7E3 antibody of Bode et al. based on the teachings of Barbas et al because the entire Fab-9 antibody would be necessary according to the teachings of Bode et al., not an optimized surface loop as claimed in the present invention.

Furthermore, although Barbas et al. teach that a small non-optimized section of a protein surface loop can be substituted into an antibody complementarity determining region where it can be optimized, Barbas et al. do not teach that an optimized protein surface loop, or a peptide mimetic based on an optimized surface loop can be linked to a therapeutic or diagnostic functional entity. Thus, an artisan would not have been motivated to utilize the teachings of Gordon et al. to produce a peptide mimetic based on an optimized surface loop that binds a specific target to arrive at the claimed invention based on the Barbas et al. reference.

Applicants have demonstrated herein that there is no teaching or suggestion in Bode et al., Barbas et al., Todd et al., Johannessen et al. or Gordon et al. of a targeted therapeutic or diagnostic agent comprising a therapeutic or diagnostic functional entity linked to an isolated peptide mimetic which is based on an optimized protein surface loop and wherein the mimetic specifically binds a selected target, and therefore, Applicants believe this rejection has been overcome as it applies to amended Claim 1 and dependent claims 4-24 and respectfully request its withdrawal.

As amended herein, claim 3 recites a protein comprising a grafted optimized protein surface loop that specifically binds a selected target, wherein the protein surface loop is not endogenous to the protein, replaces a surface loop on the protein and is optimized prior to grafting. Support for this claim can be found on page 7, lines 15-17, on page 34, lines 21-24 and elsewhere throughout the specification.

Applicants respectfully point out that although Barbas et al. teach that a small non-optimized section of a protein surface loop can be substituted into an antibody complementarity determining region where it can be subsequently optimized, Barbas et al. do not teach that a protein surface loop can be grafted into a protein after optimization. Specifically, Barbas et al. teach optimizing a surface loop after it has been grafted in a non-optimized state onto the complementarity determining region of an antibody. As Barbas et al. teach that a surface loop is optimized only after grafting and not prior to grafting, Barbas et al. do not disclose or suggest a protein comprising a grafted optimized protein surface loop that specifically binds a selected target, wherein the protein surface loop is not endogenous to the protein, replaces a surface loop on the protein, and is optimized prior to grafting. Therefore, one skilled in the art would not have been motivated to combine the teachings of Todd et al., Bode et al., and Johannessen et al., which do not mention or suggest any form of optimization or protein loop grafting with Barbas et al. to obtain the protein of claim 3. Thus, Applicants believe that the present rejection has been overcome and respectfully request its withdrawal as it pertains to Claim 3 and its dependent Claims 13-24 and 65.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending claims in this application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A check in the amount of $435.00 and a Request for an Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231, on the date shown below.

Mary L. Miller — May 12, 2000
Mary L. Miller — Date